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Review Article

Effectiveness of Gum Arabic in Diabetes and its Complications: A Narrative Review

Suzy Munir Salama[1], Hammad Ali Fadlalmola[2], Manal Mohammed Abdel Hafeez[3], Samia Ali Mohamed Ahmed[4], Rafiah Awad Mohamed[5], Nora Mohammed Ali Elatta[6], and Abdalbasit Adam Mariod[7]

[1]Indigenous Knowledge and Heritage Center, Ghibaish College of Science and Technology, Ghibaish, Sudan
[2]Nursing College, Taibah University, KSA
[3]Department of Family Education, Umm Al-Qura University, KSA
[4]Police Hospital Diabetic Center, Khartoum, Sudan
[5]College of Family Science and Community Development, International Africa University, Sudan
[6]College of Nursing Science, Omdurman Islamic University, Sudan
[7]College of Sciences and Arts-Alkamil, University of Jeddah, Alkamil, KSA

ORCID:
Suzy Munir Salama: https://orcid.org/0000-0003-0430-1436
Hammad Ali Fadlalmola: https://orcid.org/0000-0002-5065-9626
Manal Mohammed Abdel Hafeez: https://orcid.org/0000-0003-2451-9651
Samia Ali Mohamed Ahmed Fayet: https://orcid.org/0000-0001-7172-4215
Rafiah Awad Mohamed: https://orcid.org/0000-0002-3025-2351
Nora Mohammed Ali Elatta: https://orcid.org/0000-0002-9792-6744
Abdalbasit Adam Mariod: https://orcid.org/0000-0003-3237-7948

Corresponding Author: Suzy Munir Salama; email: s.salama999@hotmail.com

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Abstract

Gum Arabic (GA) is a gummy exudation from *Acacia* species, rich in soluble fibers. It is a dietary fiber used traditionally by the natives of many countries of the Arabian Peninsula, Pakistan, and India as therapeutic natural product for treating various diseases including kidney diseases, impotence, obesity, and epilepsy. Diabetes represent a global health problem causing many complications and health risk to people of different ages. The current study aimed at identifying the role of Gum Arabic in treating diseases especially diabetes. Many studies have been conducted on the role of Gum Arabic in experimentally induced diabetes as well as randomized clinical studies. This narrative review was written based on a database search in common libraries such as PubMed, Cochrane, Web of Science, and Scopus. The libraries were searched for English articles published between 1995 and 2020 focusing on the role of Gum Arabic in different preclinical and clinical trials of early and advanced level of diabetes.

Keywords: Gum Arabic, diabetes, animals, human, nanoparticles

1. Introduction

Gum Arabic (GA) is an air-dried glutinous or gummy exudation obtained from the branches and trunks of *Acacia* species, mainly *Acacia senegal* (Hashab), and a nearly associated *A. seyal* (Talha) species, which belongs to the Fabaceae family. Both species are naturally grown in the African Belt. Nigeria, Sudan, and Chad are the main gum-producing countries. GA tree is a familiar medicinal plant in Arabian Peninsula, Pakistan, and India. Gum is a nonviscous secretion that contains high percentage of soluble fibers collected principally from the *A. Seyal* and *A. Senegal* trees. The quality of GA extracted from *A. Senegal* is considered of the highest quality while those extracted from *A. seyal* as of the lowest [1]. GA is normally produced and collected from a five-year age-ripened tree which is selected when hard nodes are formed on the branches from the dried gum [2].

GA exhibits surprising chemical composition which have been elucidated by several studies. GA is composed from complex neutral or acidic polysaccharide that is formed from mixed magnesium, calcium, and potassium salt derivative of the polysaccharide acid. The units 1,3-connected β-d-galactopyranosyl form the main chain of the polysaccharide acid, while 2–5 units of 1,3-connected β-d-galactopyranosyl form the side chains. The side chain is connected to the main chain by 1,6-linkages. In addition, the units β-d-glucopyranosyl and 4-O-methyl-β-d-glucopyranosyl constitute the end of the main and side chains of the polysaccharide acid, respectively. GA has changeable chemical composition depending on some factors such as the species and age of the tree, climate, and structure of the soil. Mariod (2018) found that although, all types of GA contain a similar composition of carbohydrates, where the percentage of reducing sugars in the type of *A. senegal* was higher, they differed in their content of proteins [3]; the composition of amino acids and the percentage of protein in gum of *A. senegal* was 3% while the percentage of secondary compounds was 3–6%. The percentage of mineral salts was 3–5%, while the average ash content was 3.27% [3].

Neither the stomach nor the small intestine are able to digest the soluble dietary fiber constituent of GA. Therefore, fermentation of GA by the intestinal bacteria reflects its prebiotic characteristic of GA and its capability of increasing the Bifido bacteria. Supplementation of the consumer with 10 gm of GA on daily basis can have prebiotic potential as reported by [4].

At the homeostasis level, metabolic disturbance of proteins, lipids, and carbohydrates causes two types of diabetes; type I diabetes where beta cells of the pancreas are unable to manufacture sufficient insulin or type II diabetes where the produced endogenous insulin is irresponsive [5]. According to the World Health Organization (WHO), chronic diabetes is growing very fast globally showing twofold increase between the years 1980 and 2014. Additionally, about 50% of the deaths were hyperglycemic and below the age of 70 [6]. Oxidative stress plays key role in diabetic disorders *via* the increase in the ratio of oxidants/antioxidants leading to damage of biological macromolecules (proteins, carbohydrates, fats, and nucleic acids) which generates more reactive oxygen species and progressive cellular damage [7].

Traditionally, GA has been used in treating many health disorders such as impotence, hyperglycemia, weight increase, epilepsy, etc. [1]. GA has great intestinal tolerance and the significantly fewer side effects compared to other substrates used as prebiotic. The rapid interest in GA treatment globally came from its potency in the treatment of many ailments and their complications as well in addition to its safety and economical low cost. GA was found to be biologically active natural product due to its immunity-enhancement, antimicrobial, antihepatotoxic, antiulcer, anti-inflammatory, antioxidant, anti-mutagenic, and anti-cancer properties. It reduces glucose levels by increasing the stool's mass, reducing stool water content, trapping bile acids, and enhancing vital activities of the body [8]. At the industry level, GA showed thickening, emulsification, and stabilizing characteristics. Therefore, it is accepted in food industry as having a distinctive taste [9].

Induced diabetes mainly causes increase in blood sugar and HbA1c. In addition, serum urea and creatinine, triglycerides, low-density lipids (LDL), malondialdehyde (MDA) are elevated. On the other hand, reduction of high-density lipids (HDL), glutathione level (GSH), catalase (CAT), and superoxide dismutase (SOD) activities are significantly recorded. At the histological level, kidneys from experimentally induced diabetes in rats displayed highly significant changes in the glomerular and tubular parts of diabetic kidneys. Although the results obtained experimentally were abnormal, supplementing diabetic rats with GA revealed significant hypolipidemia, hypoglycemia, and antioxidant activity in comparison with the control group with no effect on the blood level of urea and creatinine [10]. Intake of GA in parallel with insulin altered the negative effects of diabetic mellitus on the blood biochemistry and the tissue histology as well [10].

2. Materials and Methods

Based on [11], the present narrative review was conducted by searching for related articles in the common libraries such as PubMed, Cochrane, Web of Science, and Scopus published between 1995 and 2020 using the keywords "gum Arabic," "gum Acacia," "gum Arabic-nanoparticles," "diabetes," "complications of diabetes," or "chronic diabetes." We concentrated our search on English studies that include experimentally induced diabetes and clinical cases with different stages of complications showing the efficacy of GA supplementation on early as well as advanced stages of diabetes.

3. Results

The articles' findings on the potential activity of gum Arabic in different types of preclinical and clinical studies were significantly concentrated and interpreted. Additionally, the mechanistic outcomes from the different studies on the effectiveness of gum Arabic in diabetes were illustrated and summarized on figures for better understanding.

4. Discussion

Diabetes mellitus (DM) is a chronic illness with steadily increasing frequencies in all countries [12], microvascular and macrovascular complications of diabetes that may result in mortality and morbidity [13]. Prevention and early treatment of hyperglycemia is able to delay the occurrence of complications and improve the life status of diabetic patients.

4.1. Role of GA in reducing lipid profile and obesity

Studies suggest that patients who were given 30 mg of GA mixed with 20 mg of atorvastatin have recorded remarkable reduction of their lipid profile after one month of intervention compared to those given atorvastatin only [14]. A study on broiler chickens has shown that the intake of diet supplemented with 5% and 7.5% GA has a hypolipidemic effect *via* reduction of serum cholesterol and triglycerides [15]. Another published study reported that mice fed with diet rich in fat together with 7% GA for about four and half months had a significant reduction in serum cholesterol and triglycerides. Scientists have referred the hypolipidemic efficacy of GA to different mechanisms. One pathway suggests that GA increases bile salts' excretion in the stool resulting in the consumption of cholesterol by the liver in manufacturing new bile salts and reduction of body fat together with serum cholesterol [16, 17]. Further, GA in the diet given to the mice down-expresses the genes responsible for formation of cholesterol and over-expresses the genes involved in fat oxidation in the body of mice [18]. Another mechanism of GA in reducing lipid profile was suggested by Jangra *et al.* [18] who mentioned that over-expression of fasting-induced adipose factor (FIAF) gene in the mice fed with GA induces lipolysis process and reduces the accumulation of fat in their bodies. The contribution of FIAF gene responsible for modulating lipid metabolism in type II diabetes has been supported by other studies [19, 20].

Studying antidiabetic potential of GA on alloxan-induced diabetes in experimental rats given single intraperitoneal injection dose of alloxan (105 mg/kg) revealed significant hypoglycemic effect. Based on the studies, the lowest concentration of GA showed effective improvement in body weight gain and the serum contents of albumin, total protein urea and creatinine in experimentally induced diabetic rats. Additionally, GA altered the negative effect on the relative weight of rats' internal organs [21].

Dyslipidaemia in patients with type II diabetes presents high effect on the cardiovascular health. It was claimed that GA could be a beneficial supplementation in diabetes type II patients [22]. Babiker *et al.* [23] reported that supplying diabetic patients with GA, 30 gm daily for three months was influential in reducing body weight and regulating fatty tissue problem. Also, the tested dose has increased HDL and decreased triglyceride blood levels reducing the risk of CV agents in diabetic patients.

4.2. Role of GA in reducing fasting plasma glucose and HbA1c

Documented studies suggested that GA has antidiabetic effect in human and animals as well. Addition of GA at a dose of 10 gm per day for 16 weeks to the diet of experimental prediabetics and diabetics recorded noticeable suppression in fasting blood glucose level and glycated hemoglobin (HbA1c) as well. The study revealed that GA treatment has recorded increased excretion of urinary Ca^{2+} and decreased plasma level of phosphate and urea [13]. Recent studies explained the therapeutic effect of GA reporting that ingestion of 60 gm of GA on a daily basis for 90 days can induce minor decrease in the body mass index (BMI) of diabetics, and slight change in their glycated hemoglobin (HbA1c). This may be attributed to increased intake of carbohydrates in 60% of the respondents and disrespect of 32% of participants to the regular ingestion of GA dose prescribed [24].

Babiker et al [25] observed the beneficial effect of GA in glycemic control diabetic patients receiving 30 gm of gum for four months. GA has an intrinsic glycemic index of proximately zero since it is not absorbed in small intestine [26], while Ibrahim *et al.* [24] published that in type II diabetic patients, ingestion of 60 gm/day of GA produced no significant or appreciable effect on blood glucose concentration and BMI.

4.3. Role of GA in diabetic oxidative stress

Based on many researches, oxidative stress is involved in the pathogenesis of diabetes [27] including diabetic hepatopathy [28]. In addition, oxidative stress plays an effective role in diabetic retinopathy through lipid peroxidation, DNA damage, and apoptosis of endothelial retinal cells resulting in ocular diseases such as cataract and glaucoma [29]. Further, hyperglycemia induces oxidative stress by shifting glycolysis process to hexosamine pathway that increases the formation of diphosphate-N-acetyl glucosamine [30] enhancing the production of defective genes responsible for magnification diabetes complications [31]. Intervention dose of GA, 15% in drinking water for 60 days, was proved to alter the complications of type I diabetes resulting from elevated damage produced from alloxan monohydrate-induced oxidative stress induced in rats. GA protected the diabetic liver *via* enhancement of antioxidant enzymes' overexpression. Hepatic SOD and glutathione peroxidase (GPx) were considerably overexpressed and MDA level was remarkably reduced in the hepatic tissue of diabetic animals [7].

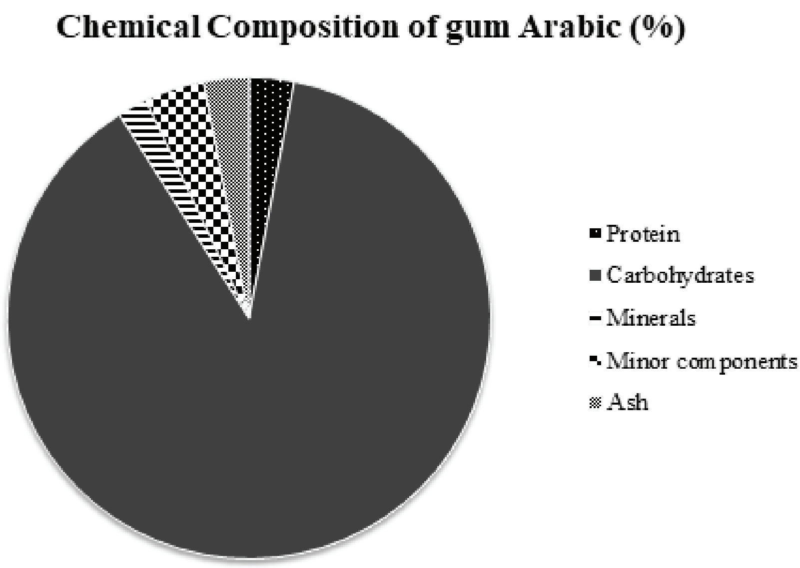

Figure 1: Chemical composition of gum Arabic (*Acacia Senegal*).

4.4. Role of GA in kidney problems

Nephropathy is considered one of the diabetic complications resulting in renal failure. Cytokines were found to play major role in the renal complications in diabetes including renal nephropathy. Transforming growth factor TGF-β1 is a pro-fibrotic protein and one of the cytokine indicators in the pathogenesis of kidney problems [32] in diabetic patients via stimulation of Collagen IV leading to fibrosis in the kidney and sclerosis in the glomeruli which eventually causes kidney failure as previously published [32, 33]. Researchers showed that the intake of 10% GA in drinking water reduced the

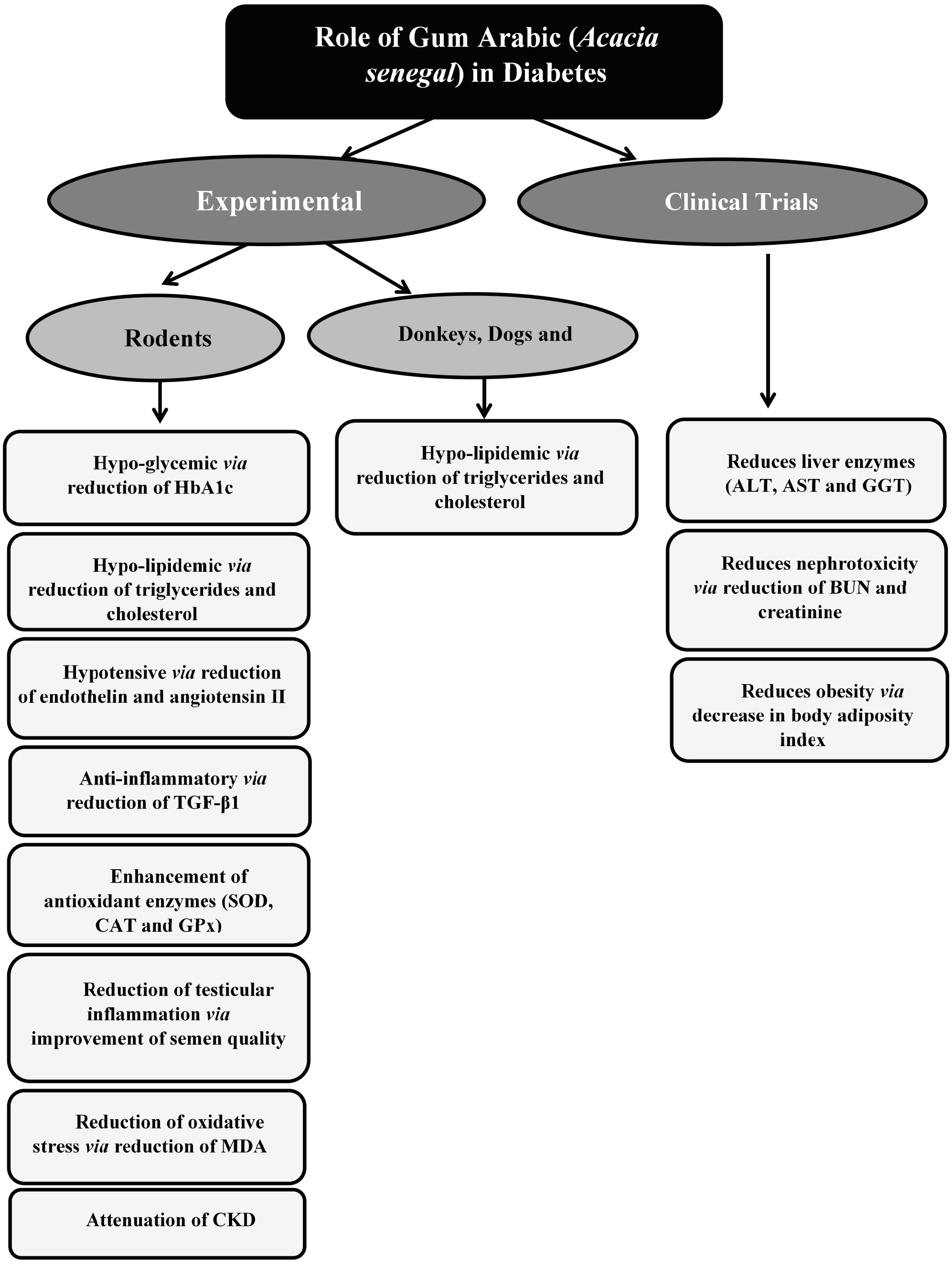

Figure 2: The role of Gum Arabic (*Acacia Senegal*) in diabetes. ALT: alanine aminotransferase; SOD: superoxide dismutase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CAT: catalase; GGT: gamma glutamyl transferase; CKD: chronic kidney failure; GPx: glutathione peroxidase; HbA1c: glycated hemoglobin; MDA: malondialdehyde; TGF-β1: transforming growth factor beta 1.

overexpression of renal TGF-β1in streptozotocin (STZ)-induced diabetic mice when treated for a month [33].

Qureshi *et al.* [34] and El Tobgy [35] found that in the investigation on diabetic rats the anti-hyperglycemic influence of GA mediated by a decrease in intestinal glucose absorption decreased the plasma glucose level, and thus the insulin level. In Addition to that, consumption of GA decreased urinary volume and glucose urea. The preventive and protective impact of GA with respect to the complications of diabetes was documented. GA improved neuropathy [36], nephropathy [7] and albuminuria. In addition, it significantly reduced serum phosphate concentration, proteinuria, and improved glomerular filtration rate which eventually progress renal functions [10].

Al Za'abi *et al.* [37] reported that adenine-fed rats showed significant decrease in body weight along with increase in diet intake and urination. At the biochemical level, the study revealed increase in the ratio between albumin/creatinine in urine and elevation in the plasma level of creatinine, urea, phosphorus, and indoxyl sulfate. Additionally, induced diabetes by alanine mixed with STZ further worsened most kidney parameters assessed. GA has considerably reduced the damage in the biochemistry and histopathology profiles of the kidney caused by adenine or adenine mixed with STZ. A recent study also reported that GA could protect the rats from renal toxicity induced by colistin [38]. Experiments on diabetic dogs and cats showed that supplementation of these animals with fermentable fibers such as GA could enhance insulin secretion through increase in short chain fatty acids which accordingly increase the production of glucagon-like peptide-1 (GLP-1) [39].

4.5. Role of GA in Diabetic Hyperphosphatemia

Hyperphosphatemia is one of the main factors of death probabilities in chronic renal diseases and renal nephropathy. Diet rich in phosphorus-binding agents were found to have potential effect in reducing absorption of phosphorus in the small intestine of diabetic patients with chronic renal problems. GA was proved to be one of these agents due to its high ability to bind to phosphorus and reducing the hazardous effects of phosphorus absorption on kidneys [40]. Recently, Farman *et al.* [41] stated that supplementation of chronic renal failure patients with GA, 30 gm daily for 180 days noticeably suppressed serum content of phosphorus.

4.6. Role of GA in Stomach Gastroparesis

Gastrointestinal problems are considered one of the complications of high blood glucose in diabetic patients [42]. Stomach gastroparesis is a disorder in long-term hyperglycemic patient that causes different degrees of weakness in the stomach motility, gastric paralysis, and delay in stomach emptying [43]. Previous studies have reported that GA protects the stomach against gastroparesis induced by uremia in rats [44]. Additionally, GA as a soluble fiber and due to its polysaccharide constituent was recently suggested to have significant effect on reducing the symptoms of stomach gastroparesis in diabetic patients [45].

4.7. Role of GA in diabetic testicular degeneration and erectile dysfunction

Complications of diabetes are accompanied by erectile dysfunction and impotence due to disruption in the nervous or vascular communication [46]. GA possesses high antioxidant capacity and is applied in researches in inhibiting the toxic impact of type I diabetic rats on reproductive male organs. Treating experimental animals with GA has successfully ameliorated the histology alterations observed on the testicular tissue of rats. Experimental data revealed that GA remarkably improved the injurious changes of testes [47]. Another study showed that consumption of GA resulted in decreased lipid peroxidation, amelioration in degenerative testicular tissue of alloxan-induced diabetic rats, and enhanced sperm quality, activity of the endogenous antioxidant enzymes together with their expressed proteins were collectively found to be increased. These effects might have roles in the treatment of reproductive problems in diabetic males [48]. A recent study reported that GA effectively enhanced male fertility [49].

4.8. Role of GA in wound healing and diabetic foot

Diabetes is accompanied by induction of abnormalities in neural and vascular structure and function as a complication symptom [50]. Consequently, inhibition of angiogenesis and amputated diabetic foot are clearly symptomized in chronic hyperglycemia [51]. Recently, studies showed that dressing wounds with hydrogel prepared from GA polysaccharides enhanced wound healing in rats through its antioxidant capacity [52].

4.9. Role of GA in diabetic neuropathy

Pathogenesis of diabetes related to hyperglycemia was suggested to be linked to autonomic neuropathy that may lead to gastrointestinal dysfunction [53]. Hailah *et al.* [54] reported that GA improved experimental diabetic peripheral neuropathy as evidenced biochemically through improvement of lipid profile and antioxidant indices, and sciatic nerve histopathology. Further, Dowidar *et al.* [55] published that GA reduced the complications resulting from type II diabetes initiated by supplementing the diet of rats with high fat and high fructose for three 3 months. GA revealed a remarkable alleviation of insulin resistance and suppression of glucagon secretion and lipid parameters.

4.10. Role of GA in diabetic cardiomyopathy

At the research level, one of the main reasons of mortality among diabetic patients in developing countries is long-term hyperglycemic complications in cardiovascular system resulting in cardiomyopathy [54]. Based on the study of Jia *et al.* [55], hyperglycemia is associated with cardiac hypertrophy *via* microvascular dysfunction. Mechanistically, increase in blood glucose level for long term in diabetic subjects leads to cardiac insulin resistance [56], stress due to oxidants, and deterioration of calcium conduction in the mitochondria due to mitochondrial dysfunction [57]. Recently, one study stated that GA reduced the progress of diabetic cardiomyopathy (DCM) through the improvement of hyperglycemia, hyperlipidemia-mediated oxidative stress. For that, it may have the therapeutic potential of GA for human DCM [58]. Studies published that heat shock protein (Hsp_{20}) was proved to have an impact in cardiac injury stimulated by long-term hyperglycemia through restoration of cardiac dysfunction [59]. The anti-inflammatory efficacy of Hsp_{20} protects against overproduction of cytokines of inflammation implicated in cardiac hypertrophy [60]. Additionally, increased secretion of Hsp_{20} by cardiomyocytes has been induced by GA intervention in diabetic rats for eight weeks resulting in altering the status of diabetic cardiomyopathy [61]. Another report stated that adding GA 15% to drinking water of mice for one month protected their hearts from the injurious effect of water pipe smoke *via* its significant reduction of pro-inflammatory cytokines and stress due to oxidants [62].

Cardiovascular diseases (CV) are incidentally increasing in people with type II diabetes [63]. Previously, Glover *et al.* (2009) published that supplementing diet with dietary fiber, including GA has resulted in significant decrease in the average value of systolic blood pressure in normal individuals [64].

4.11. GA and nanoparticles

Ashraf *et al.* exposed that GA capped-silver nanoparticles exhibited inhibitory effect on the advanced glycation end products that contribute in the pathology of many diseases such as diabetes, Alzheimer's disease, and eurosclerosis. Recently, silver nanoparticles biosynthesized from a mixture of three aqueous extracts – GA, parsley, and corn silk – showed significant antioxidant activity through increased blood level of glutathione in alloxan-induced DM in experimental rats [65]. Studies published that nanoparticles formed from GA and maltodextrin showed significant antioxidant power in reducing oxidative stress in diabetes [66, 67]. Another study reported than nanoparticles prepared from chitosan and GA showed significant activity in bone regeneration in rabbits [68]. Nanoparticles formed from GA and *Calindula officinalis* has proved *in vitro* potential activity in wound healing and skin engineering *via* enhancement of fibroblast cells proliferation [69]. Additionally, silver nanofibers prepared from GA has recently showed significant antimicrobial wound healing activity due to the improvement to the proliferation of fibroblast cells of mouse embryos *in vitro* [70].

5. Conclusion

Food supplementation with GA reduces blood sugar level and glycated hemoglobin HbA1C in prediabetic and diabetic small experimental rats via its hypolipidemic, anti-inflammatory activities, and enhancement of antioxidant enzymes. In addition, GA suggested hypoglycemic effect through its activation to insulin secretion. Moreover, randomized clinical trials revealed significant efficacy of GA supplementation in ameliorating serum glucose level.

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Ethical Considerations

Not applicable.

Availability of Data and Material

All the data and materials of the present narrative review are mentioned in the manuscript and clearly cited in the body text along with the references section.

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Competing Interest

Authors declare no conflict of interest.

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